ELSEVIER

Journal of Organometallic Chemistry 661 (2002) 159–167

Journal of Organometallic Chemistry

www.elsevier.com/locate/jorganchem

# Selective reactions of transition-metal-generated radicals

Torsten Linker *

*Department of Chemistry, University of Potsdam, Karl-Liebknecht-Strasse 24-25, D-14476 Golm, Germany*

Received 25 April 2002; accepted 29 July 2002

Dedicated to Professor Helmut Werner on the occasion of his retirement in recognition of his tremendous contributions to organometallic chemistry

**Abstract**

In this microreview, we describe selective radical reactions in the presence of potassium permanganate, $Mn(OAc)_3$, and cerium(IV) ammonium nitrate (CAN), which were developed in our group during the last years. The in situ generation of manganese(III) by potassium permanganate results in a low concentration of the oxidant, and allowed the chemoselective synthesis of H-atom transfer products in good yields. Furthermore, tandem reactions were developed to afford bicyclooctanes in diastereomerically pure form. Manganese(III) acetate was the reagent of choice for the selective synthesis of oxidation products. Ultrasonic irradiation remarkably accelerated such radical reactions and the method was applied for the simple and selective synthesis of tetra-acceptor-substituted alkenes from commercially available malonates. Due to the mild reaction conditions, CAN was superior to $Mn(OAc)_3$ for applications in carbohydrate chemistry. Thus, 2-*C*-branched carbohydrates were synthesized from glycals in only one step and in excellent yields. The radical additions afford exclusively one regioisomer and exhibit a high degree of stereoselectivity. Finally, the anomeric radicals are trapped by CAN via a direct ligand transfer, which is important for the mechanistic understanding of transition-metal-mediated radical reactions.


*Keywords:* Transition metals; Radicals; Selectivity; CH-acidic compounds; Carbohydrates

## 1. Introduction

The transition-metal-mediated generation of radicals by single electron transfer is of current interest in organic chemistry [1]. The advantage over traditional radical reactions is the oxidative or reductive termination of the non-chain processes with the introduction of functionality into the products. Furthermore, modern methodologies apply transition metals, to avoid the high toxicity of tin or mercury compounds. The radicals can be generated from uncharged starting materials by electron transfer via the corresponding radical ions and subsequent elimination of a halide or a proton (pathway A), or by direct reduction of cations or oxidation of anions (pathway B) (Scheme 1).

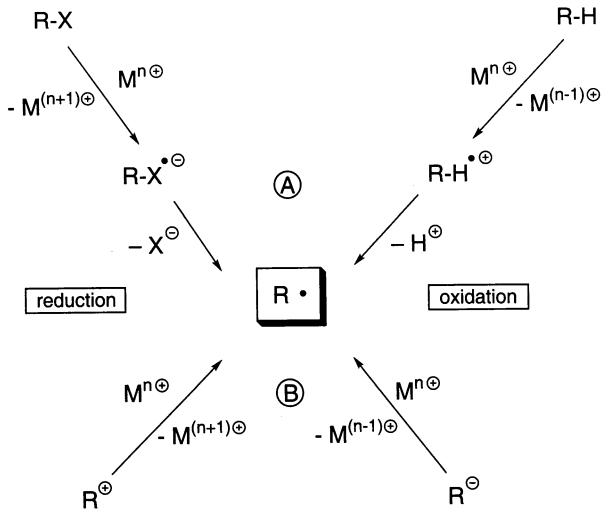
Samarium(II) iodide is the reagent of choice for the reductive generation of radicals from halides or ketones. During the last decade, many synthetic applications were developed, which were recently summarized in excellent reviews [2]. For the oxidative generation of radicals manganese(III) acetate has received most attention [3]. However, other metals in high oxidation states were applied as oxidizing agents, and especially cerium(IV) became more and more attractive for radical C–C bond formations very recently [4]. The disadvantage of metal-mediated radical reactions often consists in low chemoselectivities, with the result of complex product mixtures. This microreview will focus on selective radical reactions in the presence of manganese(III) and cerium(IV), which were developed in our group during the last years.

## 2. Mechanistic considerations

The mechanism of the oxidative generation of radicals by transition metals was intensively investigated during the last years [1]. A broad variety of CH-acidic

* Tel.: +49-331-9775212; fax: +49-331-9775056
*E-mail address:* linker@chem.uni-potsdam.de (T. Linker).

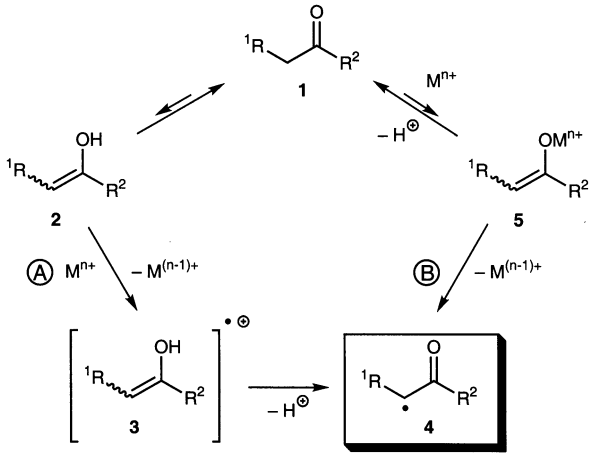
0022-328X/02/$ - see front matter 
PII: S0022-328X(02)01824-7



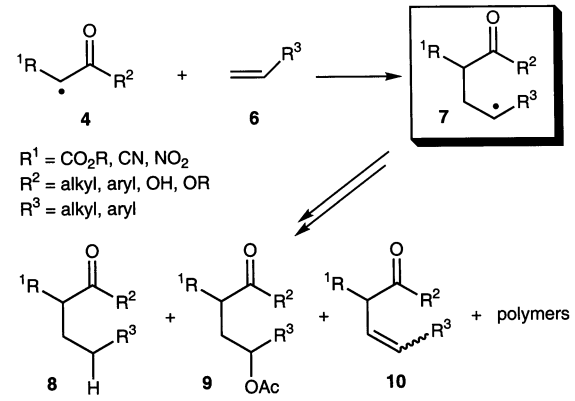

Scheme 1.

compounds **1** may serve as precursors for such reactions, which afford radicals **4** under electron transfer conditions. Early studies by Fristad pointed out, that the rate of radical generation correlates with the enolizability of the substrates **1** [5]. Thus, electron-withdrawing groups $R^1$ ($CO_2R$, CN, $NO_2$) accelerate the reactions remarkably. However, if a single electron transfer from the enol form **2** to the metal in a high oxidation state affords radical cations **3** (pathway A), or if the reactions proceed in the ligand sphere of the metal via enolates **5** (pathway B) is still a matter of debate (Scheme 2).

Due to the acceptor substituents, the radicals **4** exhibit electrophilic character and add readily to electron-rich alkyl- and aryl-substituted alkenes **6** (Scheme 3). The advantages of this method are the simple precursors and the low toxicity of the reagents. However, the adduct




Scheme 2.




Scheme 3.

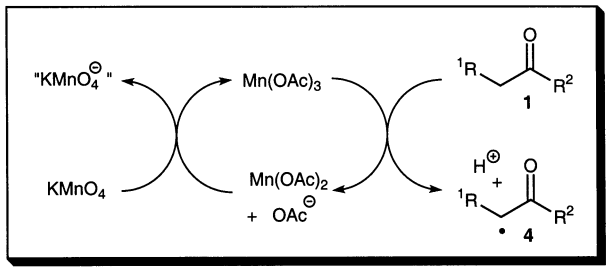
radicals **7** can react further by various pathways, resulting in complex product mixtures. Depending on the substrates and reaction conditions, hydrogen-atom transfer products **8** compete with acetates **9** and alkenes **10**. Finally, formation of oligomeric and polymeric material reduces the yields of the reactions. To overcome these problems, Snider developed elegant manganese(III)-mediated radical cyclizations, which exhibit higher chemoselectivities [3c]. Furthermore, if the reactions were performed in the presence of cuprous(II) acetate, alkenes **10** can be isolated selectively. However, no good method for the synthesis of H-transfer products **8** by intermolecular radical additions existed in literature. Our aim was to develop a new methodology for this purpose, based on the cheap oxidant potassium permanganate.

## 3. Potassium permanganate-mediated radical reactions

The synthesis of manganese(III) acetate by the oxidation of $Mn(OAc)_2$ with potassium permanganate is a well-known process (Eq. (1)). Our approach was based on the in situ

$$4Mn(OAc)_2 + KMnO_4 + 8HOAc \rightarrow 5Mn(OAc)_3 + KOAc + 4H_2O \quad (1)$$

generation of $Mn(OAc)_3$ by $KMnO_4$ in the presence of the CH-acidic precursor **1** (Scheme 4). Only catalytic

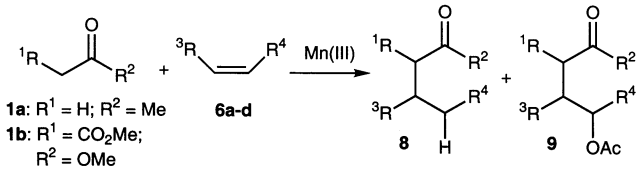



Scheme 4.

amounts of manganese(III) are involved in this reaction cycle, which allows the generation of the radicals **4** under 'non-oxidative conditions'. Thus, the hydrogen-atom transfer products **8** might be synthesized selectively without competing oxidations to acetates **9** or alkenes **10**. A similar protocol was developed by the electrochemical regeneration of $Mn(OAc)_3$ from manganese(II) [6], but the potassium permanganate-mediated radical reactions are characterized by easily accessible and cheap starting materials and a simple preparative set up. Furthermore, the required amount of manganese is reduced drastically, since one equivalent of potassium permanganate can generate five equivalents of $Mn(OAc)_3$ and, thus, five equivalents of radicals.

To demonstrate the applicability and selectivity of potassium permanganate in radical reactions, we chose acetone (**1a**) and dimethyl malonate (**1b**) as CH-acidic precursors. The addition to various alkyl-substituted alkenes **6a**–**d** in the presence of $KMnO_4$ (method A) was compared with the conventional manganese(III) acetate procedure (method B) (Table 1, Scheme 5) [7].

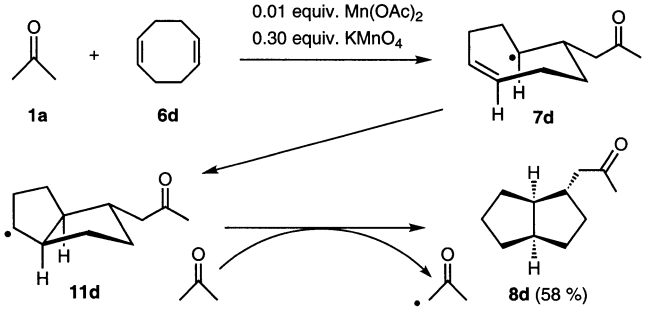
As shown in Table 1, the advantage of method A for the alkyl-substituted olefins **6a**–**d** is obvious, since the H-atom transfer products **8** are formed selectively (entries 1, 3, 5, 7, 9, 11, 13, and 15). In contrast, $Mn(OAc)_3$-mediated additions afford product mixtures (entries 2, 4, 6, 8, 10, 12, 14, and 16). Interestingly, the alkenes did not react to diols with potassium permanganate, which can be rationalized by the fast electron transfer from manganese(II) acetate to the oxidant. The only by-product with both procedures was oligomeric material, which was easily removed by column chromatography. The high chemoselectivity obtained with method A can be explained by the low concentration




Scheme 5.

of manganese(III) in the reaction cycle. Thus, the oxidation to the acetates **9** cannot compete with hydrogen-atom transfer. Therefore, our new protocol allowed the selective synthesis of the desired products **8**. Furthermore, the required amount of manganese is reduced drastically by employing $KMnO_4$ in radical reactions, since one equivalent of potassium permanganate generates five equivalents of $Mn(OAc)_3$.

Cyclooctadiene (**6d**) represents an interesting substrate for potassium permanganate-mediated radical reactions, which is outlined for the addition of acetone (**1a**) (Scheme 6) [7a]. The initially formed adduct radical **7d** readily undergoes transannular cyclization to the




Scheme 6.

Table 1
Radical additions of precursors **1a** and **1b** to different alkenes **6**

| Entry | Precursor **1** | Alkene **6** | Method [a] | H-Tansfer **8** (%) [b] | Acetate **9** (%) [b] |
|---|---|---|---|---|---|
| 1 | Acetone (**1a**) | 1-Octene (**6a**) | A | 49 | – |
| 2 | Acetone (**1a**) | 1-Octene (**6a**) | B | 31 | 15 |
| 3 | Malonate (**1b**) | 1-Octene (**6a**) | A | 41 | – |
| 4 | Malonate (**1b**) | 1-Octene (**6a**) | B | 13 | 38 |
| 5 | Acetone (**1a**) | Cyclohexene (**6b**) | A | 56 | – |
| 6 | Acetone (**1a**) | Cyclohexene (**6b**) | B | 25 | 19 |
| 7 | Malonate (**1b**) | Cyclohexene (**6b**) | A | 40 | – |
| 8 | Malonate (**1b**) | Cyclohexene (**6b**) | B | 8 | 25 |
| 9 | Acetone (**1a**) | Cyclooctene (**6c**) | A | 39 | – |
| 10 | Acetone (**1a**) | Cyclooctene (**6c**) | B | 23 | 16 |
| 11 | Malonate (**1b**) | Cyclooctene (**6c**) | A | 32 | – |
| 12 | Malonate (**1b**) | Cyclooctene (**6c**) | B | 9 | 41 |
| 13 | Acetone (**1a**) | 1,5-Cyclooctadiene (**6d**) | A | 58 | – |
| 14 | Acetone (**1a**) | 1,5-Cyclooctadiene (**6d**) | B | 24 | 43 |
| 15 | Malonate (**1b**) | 1,5-Cyclooctadiene (**6d**) | A | 58 | – |
| 16 | Malonate (**1b**) | 1,5-Cyclooctadiene (**6d**) | B | 5 | 54 |

[a] Method A, 0.01 equivalents $Mn(OAc)_2$, HOAc, 70 °C, slow addition of 0.3–0.4 equivalents $KMnO_4$; method B, two equivalents $Mn(OAc)_3$, HOAc, 70 °C.

[b] Yield of isolated product after silica gel chromatography.

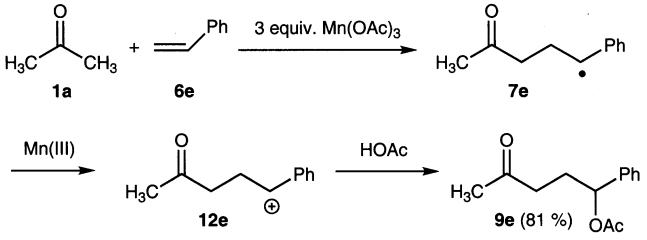
intermediate **11d** which, after hydrogen-atom abstraction, affords chemoselectively the bicyclooctane **8d** in good yield. Furthermore, the reaction exhibits a high degree of diastereoselectivity, since the *exo*,*cis*-configurated isomer was formed as the sole product. This result can be rationalized in terms of the preferred *pseudo* equatorial orientation of substituents in radical cyclizations [8].

The limit of our in situ method was reached with alkenes like styrene or stilbene, for which no C–C bond formation to products **8** was observed [7]. This result can be rationalized by the fast polymerization of aryl-substituted olefins and, thus, hydrogen-atom abstraction cannot compete. However, for alkyl-substituted alkenes the potassium permanganate-mediated radical reactions provide a valuable tool for the chemoselective synthesis of H-transfer products. Furthermore, the addition to cyclooctadiene exhibits a very high degree of stereoselectivity. Thus, the generation of radicals from other CH-acidic substrates by potassium permanganate might offer promising opportunities for future synthetic applications.

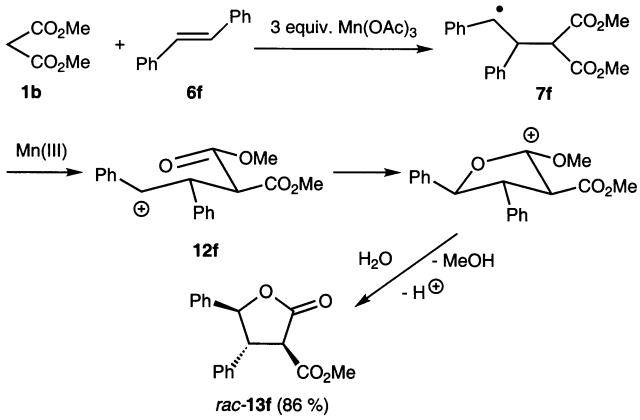
## 4. Manganese(III)-mediated radical reactions

To overcome the problem of the undesired polymerization of aryl-substituted alkenes in the presence of potassium permanganate, we subsequently became interested in the generation of radicals from acetone (**1a**) by an excess of manganese(III) acetate and investigated the addition to styrene (**6e**). The advantage of this strategy consists in the low oxidation potential of the benzylic adduct radicals **7e** ($E_{ox} \approx 0.37$ V vs. SCE) [9], which are readily oxidized to cations **12e**. Finally, trapping by the solvent acetic acid affords the acetate **9e** in high yield (Scheme 7) [7a].

Interestingly, the same methodology allows an easy and high yielding synthesis of lactone **13f**, starting from dimethyl malonate (**1b**) as CH-acidic precursor. After addition to *trans*-stilbene (**6f**), the adduct radical **7f** is again oxidized to a cation **12f**, which is obviously trapped by the carbonyl group intramolecularly (Scheme 8). The higher oxidation potential of alkyl radicals ($E_{ox} > 1.0$ V vs. SCE) compared with benzyl




Scheme 7.

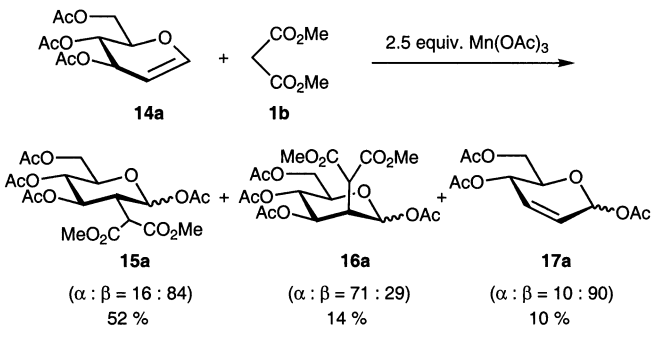



Scheme 8.

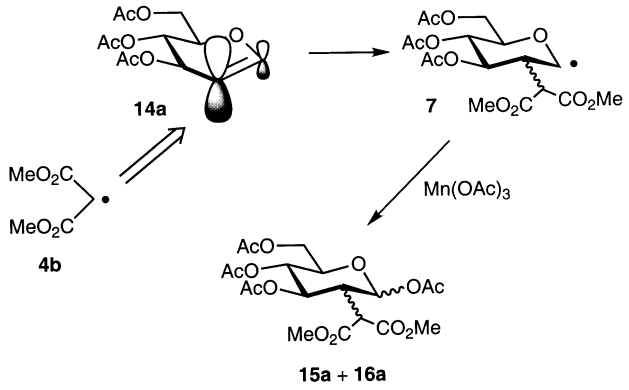
radicals ($E_{ox} \approx 0.37$ V vs. SCE) [9] explains, why only aryl-substituted alkenes undergo lactonization (see also Table 1). The high degree of stereoselectivity can be rationalized in terms of the preferred equatorial orientation of the substituents in the transition state of the cyclization. Thus, the all-*trans*-configurated lactone **13f** is formed as the sole product in 86% yield [7b].

After the successful addition of malonyl radicals to electron-rich alkenes, we became interested in reactions of higher functionalized compounds. The idea was to apply manganese(III) acetate for the first time in carbohydrate chemistry. Glycals **14** should be ideal precursors for this purpose, since these chiral building blocks can be prepared on a multigram scale or are commercially available. Therefore, we investigated the addition of dimethyl malonate (**1b**) to tri-*O*-acetyl-D-glucal (**14a**) in the presence of $Mn(OAc)_3$ (Scheme 9) [10].

Indeed, the C–C bond formation products **15a** and **16a** were obtained highly regioselectively in 66% yield. The exclusive attack of the malonyl radicals to the 2-position of the glycal can be rationalized by the mechanism outlined in Scheme 10. Due to the acceptor-substitutents, the malonyl radicals **4b** are characterized by the low energy of the SOMO and exhibit electrophilic character [11]. Thus, the interaction with the HOMO of the double bond becomes predominant,




Scheme 9.

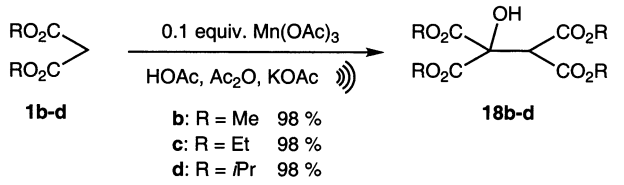



Scheme 10.

which has the largest coefficient at the 2-position of glycals. This explains the highly regioselective addition of dimethyl malonate (**1b**) to afford exclusively carbohydrate 2-*C*-analogs **15a** and **16a** and reveals the importance of orbital interactions in radical reactions. In the last step of the reaction, the anomeric radicals **7** are easily oxidized by a second equivalent of manganese(III) acetate to the final products.

The preferred formation of *gluco*-configurated products can be rationalized by a *trans* attack to the 3-*O*-acetyl group, which is in accordance with cycloadditions to glucals [12]. Presumably, the same steric effects operate at the anomeric center, where the malonyl substituent controls the reaction. Thus, the β-*gluco* and α-*manno* isomers are obtained predominantly. In summary, the manganese(III)-mediated radical addition of dimethyl malonate to glucal provides an easy route to 2-*C*-analogs of D-glucose, which is superior to literature known processes. Since a broad variety of CH-acidic precursors are available, this methodology should open up interesting prospects for future synthetic applications in carbohydrate chemistry. However, the moderate stereoselectivities and resulting product mixtures are a drawback of our new method. Furthermore, unsaturated carbohydrates **17a** are formed as by-products, due to an acid-catalyzed Ferrier rearrangement under the drastic reaction conditions [13]. Therefore, milder oxidants than $Mn(OAc)_3$ and other transition-metal-mediated radical reactions are required for the application in carbohydrate chemistry, which will be described in Chapter 5.

Another attractive alternative to further improve the yields of manganese(III)-mediated radical reactions should be provided by ultrasonic irradiation. Such reactions have attracted much attention in organic synthesis [14] and were recently applied for radical reactions as well [15]. Therefore, we investigated the addition of dimethyl malonate (**1b**) to alkenes under ultrasonic irradiation. However, the expected C–C bond formation did not take place, but the alcohol **18b** could be isolated in high yield. To further optimize this

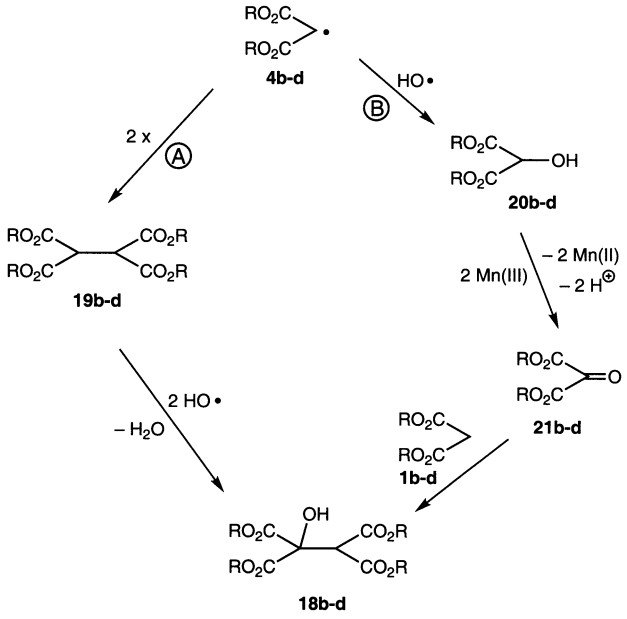



Scheme 11.

surprising reaction, we irradiated various malonates **1b–d** in the presence of $Mn(OAc)_3$ without alkenes (Scheme 11) [16].

Finally, the best results were obtained by the addition of acetic anhydride and potassium acetate to the reaction mixture, which accelerate the enolization of CH-acidic compounds and, therefore, the generation of radicals [5,7]. Under such conditions, the alcohols **18** were isolated in almost quantitative yield. Furthermore, reactions with catalytic amounts of oxidant were realized, since manganese(II) can be reoxidized to manganese(III) in acetic acid during ultrasonic irradiation [15a]. After the successful optimization of the reaction conditions with dimethyl malonate (**1b**), the diethyl malonate **1c** and the sterically more hindered diisopropyl ester **1d** afforded the desired products **18c** and **18d** in excellent yields as well [16].

The formation of the alcohols **18** can be rationalized by two different mechanistic pathways (Scheme 12). Due to the high concentration of malonyl radicals **4** generated under ultrasonic irradiation, the dimers **19** might be obtained (pathway A). Finally, oxidation to the observed products **18** by hydroxy radicals, which are always formed by ultrasonic reactions [14], is conceivable. Alternatively, the malonyl radicals **4** might be trapped directly by hydroxy radicals to afford the




Scheme 12.

alcohols **20** (pathway B), which are further oxidized to the mesoxalic esters **21** under the reaction conditions. This hypothesis is in accordance with literature known examples for the acceleration of the oxidation of alcohols by manganese salts and ultrasound [17]. Finally, the excess of malonates **1** and the ketones **21** afford the products **18** by a Knoevenagel reaction.

To differentiate between these two mechanistic pathways, the dimer **19c** was synthesized independently and then irradiated in the presence of $Mn(OAc)_3$. Even after 6 h no conversion was obtained, which excluded pathway A. Further evidence for pathway B was found by control experiments with diethyl malonate (**1c**) and diethyl mesoxalate (**21c**), which react smoothly to the alcohol **18c** under irradiation. Therefore, ultrasound not only accelerates the generation of radicals and the oxidation to the mesoxalates **21**, but also the Knoevenagel reaction.

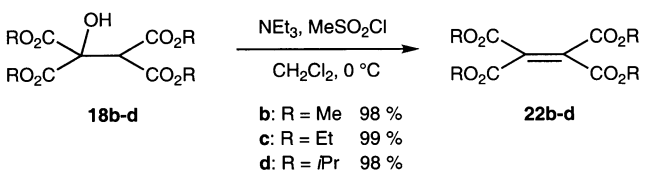
Finally, these new ultrasonic reactions are not only interesting from the mechanistic point of view, but are also important for synthetic applications. Thus, the dehydration of the alcohols **18** proceeds smoothly under mild conditions, to afford tetra-acceptor-substituted alkenes **22** quantitatively (Scheme 13) [16]. Such compounds are important precursors for Diels–Alder reactions, Michael additions, or polymerizations, but are difficult to prepare. In contrast, our new procedure allows the synthesis from cheap and commercially available malonates in only two steps in excellent yields. Since radicals can be generated from various CH-acidic substrates by manganese(III), the present methodology offers promising prospects for the synthesis of other acceptor-substituted alkenes.

## 5. Cerium(IV)-mediated radical reactions

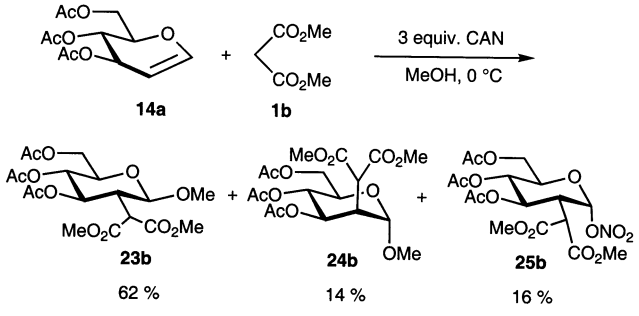
Among the various cerium(IV) complexes, cerium(IV) ammonium nitrate (CAN) is the most important oxidant in organic synthesis, since it is sufficiently stable in different solvents and is commercially available. Besides its propensity of introducing and removing protecting groups via single-electron transfer or Lewis acid catalysis [18], CAN serves as a convenient reagent for the generation of radicals from CH-acidic substrates (Chapter 2) [4]. Due to the comparable oxidation potential of CAN (+1.61 V vs. NHE) and manganese(III) acetate (+1.54 V vs. NHE), both one-electron oxidants exhibit a similar reactivity pattern. However, the advantage of CAN consists in the milder reaction conditions, which allow the generation of radicals in methanol or acetonitrile at lower temperatures. Thus, this reagent should be superior to $Mn(OAc)_3$ for applications in carbohydrate chemistry. Although CAN was used for the direct azidonitration of glycals [19], no radical C–C bond formations were described in literature.

Therefore, we investigated the addition of dimethyl malonate (**1b**) to tri-*O*-acetyl-D-glucal (**14a**) in the presence of CAN [10]. Indeed, a smooth addition of the intermediary generated malonyl radicals takes place even at 0 °C, and the formation of the undesired rearrangement products **17a** was suppressed completely. Thus, the carbohydrate 2-*C*-analogs **23**–**25** could be isolated highly regioselectively in over 90% yield (Scheme 14). Furthermore, due to the lower reaction temperature higher stereoselectivities were obtained with cerium(IV) than with manganese(III). Again, the regioselectivity of the addition is controlled by favorable orbital interactions, which is in accordance with our previous studies with $Mn(OAc)_3$ (Chapter 4).

To further increase the stereoselectivities and to elucidate the scope and limitations of our new method, other malonates and glycals were next tested. Indeed, tri-*O*-acetyl-D-galactal (**14b**) and even glycals **14c** and **14d** derived from pentoses react smoothly with dimethyl (**1b**) and diisorpopyl malonate (**1c**), and the 2-*C*-branched carbohydrates **23**–**25** could be isolated in excellent yields in analytically pure form on a gram scale (Table 2) [20]. The observed preferred attack of malonyl radicals to the double bond of the glycals can be best rationalized by steric interactions. Although the change from dimethyl malonate (**1b**) to diisopropyl malonate (**1c**) only slightly alters the α:β ratio, the substitution pattern of the glycals **14** has a strong influence on the stereoselectivity. Thus, in all examined reactions the radicals add preferentially *trans* to the acetate group in the 3-position. The highest stereoselectivities were observed with tri-*O*-acetyl-D-galactal (**14b**) and di-*O*-acetyl-D-arabinal (**14d**), since two ester groups shield the same face of the carbohydrate. Furthermore, in both cases one substituent is orientated *pseudo* axial,

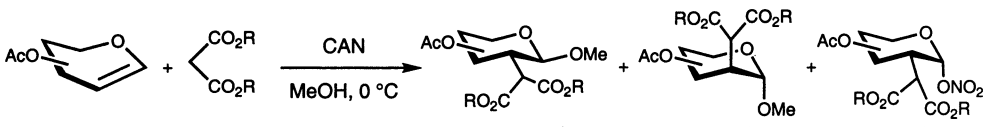


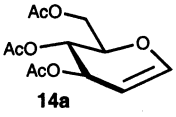
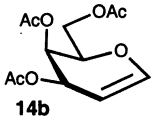
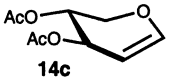
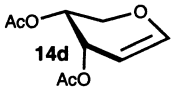

Scheme 13.




Scheme 14.

Table 2
Radical additions of malonates **1b** and **1c** to different glycals **14**




| 14 | 1 | R | *dr* α : β[a] | 23 (%)[b] | 24 (%)[b] | 25 (%)[b] |
|---|---|---|---|---|---|---|
|  **14a** | **1b** | Me | 85 : 15 | *gluco*-**23b** (62) | *manno*-**24b** (14) | *gluco*-**25b** (16) |
| | **1c** | *i*-Pr | 91 : 9 | *gluco*-**23c** (68) | *manno*-**24c** (8) | *gluco*-**25c** (16) |
|  **14b** | **1b** | Me | >98 : 2 | *galacto*-**23b** (78) | - | *galacto*-**25b** (8) |
| | **1c** | *i*-Pr | >98 : 2 | *galacto*-**23c** (73) | - | *galacto*-**25c** (17) |
|  **14c** | **1b** | Me | 93 : 7 | *xylo*-**23b** (81) | *lyxo*-**24b** (6) | - |
| | **1c** | *i*-Pr | 87 : 13 | *xylo*-**23c** (75) | *lyxo*-**24c** (11) | - |
|  **14d** | **1b** | Me | <2 : 98 | *arabino*-**23b** (89) | - | - |
| | **1c** | *i*-Pr | <2 : 98 | *arabino*-**23c** (87) | - | - |

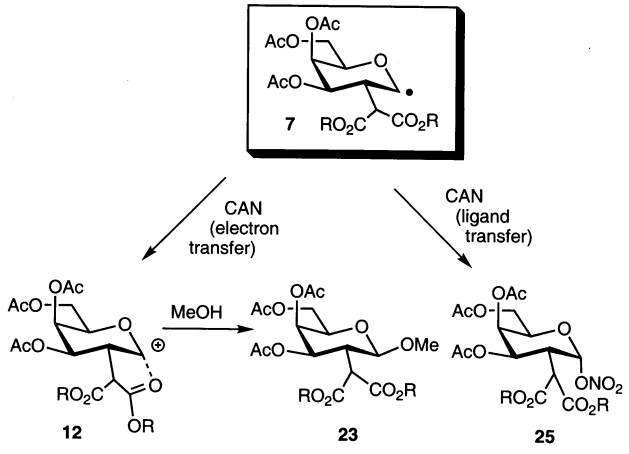
[a] Diastereomeric ratios determined by $^1$H NMR analysis of the crude product (600 MHz).
[b] Yield of isolated product after column chromatography.

which results in severe steric interactions with the malonyl radicals **4** and, thus, *galacto*- and *arabino*-configurated products are formed exclusively (Table 2) [20].

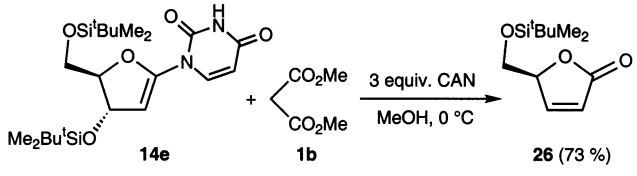
Finally, the formation of methyl glycosides **23** and nitrates **25** is interesting from the mechanistic point of view. The adduct radical **7** is readily oxidized by CAN to the cation **12**, which is trapped by the solvent to afford the methyl glycoside **23**. The exclusive formation of β-galactosides, β-glucosides, and α-mannosides **23** can be rationalized by a neighboring group participation of the malonyl substituent (Scheme 15) [20]. On the other hand, the nitrates **25** are exclusively obtained as α-anomers and cannot be formed via the intermediate **12**. A direct ligand transfer from CAN without participation of cations is more likely, which would explain the high stereoselectivity, since carbohydrate radicals like **7** are preferentially trapped from the α-face [21].

The limit of the synthesis of 2-*C*-analogs of carbohydrates in the presence of CAN was reached with the attempted addition of dimethyl malonate (**1b**) to the unsaturated furanoid glycal **14e**. This strategy would have provided a new entry to 2′-*C*-branched nucleosides. Unfortunately, due to the electron-rich double bond a fast Ferrier rearrangement [13] to the lactone **26** competes with the C–C bond formation under the strongly oxidative reaction conditions (Scheme 16) [22].

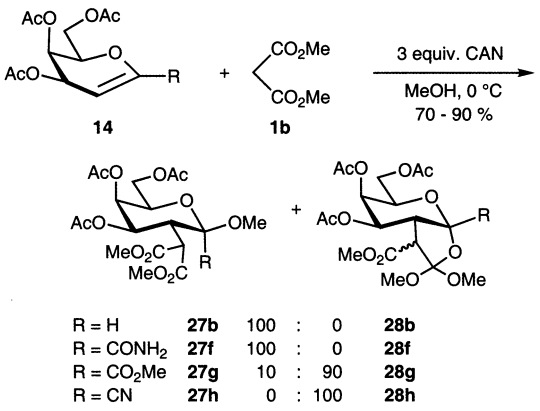
However, very recently we succeeded in the addition of dimethyl malonate (**1b**) to electron-poor glycals **14f–h** (Scheme 17) [23]. A remarkable influence of the




Scheme 15.




Scheme 16.




Scheme 17.

substituents R on the product distribution was observed, which can be rationalized by the different oxidation potentials of the intermediary formed adduct radicals. Thus, for the unsubstituted galactal **14b** and the carboxamide **14f** only the methyl glycosides **27** were obtained, whereas the nitrile **14h** affords exclusively the ortho ester **28h**. This dramatic influence of the substitution pattern at the double bond is not only interesting for synthetic applications, but sheds light on the mechanism of transition-metal-mediated radical reactions.

In summary, the addition of malonates to glycals in the presence of CAN provides a convenient route to 2-*C*-analogs of carbohydrates, which in terms of steps and yield is superior to literature known procedures. Furthermore, due to the malonyl side chain the obtained addition products might be transferred into biologically interesting modified carbohydrates. Since a broad variety of CH-acidic precursors are available and various glycals can be easily synthesized, this methodology should open up interesting prospects for future applications in carbohydrate chemistry.

## 6. Conclusion

The generation of radicals by transition metals is of current interest in organic chemistry, but the reactions often proceed with moderate chemo- and stereoselectivities. We developed a new and convenient protocol to mediate radical reactions by potassium permanganate, which exhibits several advantages over the conventional stoichiometric manganese(III) procedure. The in situ generation of $Mn(OAc)_3$ permits a low concentration of the oxidant and, thus, the H-atom transfer products were obtained chemoselectively in good yields. Additionally, cyclooctadiene has proved to be an attractive substrate for such reactions, since the radical addition afforded exclusively one diastereomer by a tandem sequence. Finally, the required amount of manganese is reduced drastically employing the in situ method and, consequently, this procedure is environmentally more acceptable.

Manganese(III) acetate was the reagent of choice for the selective synthesis of oxidation products. Thus, additions to aryl-substituted alkenes afforded the C–C bond formation products in excellent yields. Furthermore, dimethyl malonate as radical precursor provided an easy entry to the diastereoselective synthesis of lactones. Manganese(III) acetate was employed for the first time in carbohydrate chemistry, which allowed an easy and convenient synthesis of *C*-analogs. The reactions exhibit a very high degree of regioselectivity, since only 2-*C*-branched sugars were obtained. This result was rationalized by favorable orbital interactions between the SOMO of the malonyl radicals and the HOMO of the double bond. Finally, ultrasonic irradiation remarkably accelerated radical reactions in the presence of manganese(III) acetate. This method was applied for the simple and selective synthesis of tetra-acceptor-substituted alkenes, starting from cheap and commercially available malonates as precursors.

Due to the mild reactions conditions, CAN was superior to $Mn(OAc)_3$ for applications in carbohydrate chemistry. The protocol is characterized by easily available malonates and glycals as precursors, and the reactions can be performed on a multigram scale. Again, the additions exhibit a very high degree of regioselectivity, and the 2-*C*-branched sugars were obtained exclusively in excellent yields. Furthermore, the substitution pattern of the glycals strongly alters the diastereomeric ratios. Thus, the CAN-mediated addition of malonates to tri-*O*-acetyl-D-galactal and di-*O*-acetyl-D-arabinal occurs exclusively from one face of the carbohydrate. The same high degree of stereoselectivity was found during the reactions of acceptor-substituted glycals. Furthermore, the substituents at the double bond remarkably influence the product distribution, which directly reflects the oxidation potentials of the anomeric radicals. Thus, strong evidence was found for a ligand transfer rather than electron transfer, which sheds light on the mechanism of transition-metal-mediated radical reactions. Due to the high selectivities obtained with potassium permanganate and CAN, such metal complexes open up promising prospects for future synthetic applications in radical chemistry.

## Acknowledgements

This work was generously supported by the Deutsche Forschungsgemeinschaft (SFB 347 'Selektive Reaktionen Metall-aktivierter Moleküle').

## References


[1] P. Renaud, M.P. Sibi (Eds.), Radicals in Organic Synthesis, vol. 1, Wiley-VCH, Weinheim, 2001, pp. 153–228.
[2] (a) G.A. Molander, Org. React. 46 (1994) 211;
(b) G.A. Molander, C.R. Harris, Chem. Rev. 96 (1996) 307;
(c) A. Krief, A.-M. Laval, Chem. Rev. 99 (1999) 745.
[3] (a) J. Iqbal, B. Bhatia, N.K. Nayyar, Chem. Rev. 94 (1994) 519;
(b) P.I. Dalko, Tetrahedron 51 (1995) 7579;
(c) B.B. Snider, Chem. Rev. 96 (1996) 339;
(d) G.G. Melikyan, Org. React. 49 (1996) 427.
[4] (a) V. Nair, J. Mathew, J. Prabhakaran, Chem. Soc. Rev. (1997) 127–132;
(b) T. Sommermann, Synlett (1999) 834.
[5] (a) W.E. Fristad, J.R. Peterson, J. Org. Chem. 50 (1985) 10;
(b) W.E. Fristad, J.R. Peterson, A.B. Ernst, J. Org. Chem. 50 (1985) 3143;
(c) W.E. Fristad, J.R. Peterson, A.B. Ernst, G.B. Urbi, Tetrahedron 42 (1986) 3429.
[6] (a) R. Warsinsky, E. Steckhan, J. Chem. Soc. Perkin Trans. 1 (1994) 2027;
(b) H.J. Schäfer, in: P. Renaud, M.P. Sibi (Eds.), Radicals in Organic Synthesis, vol. 1, Wiley-VCH, Weinheim, 2001, pp. 250–297.
[7] (a) U. Linker, B. Kersten, T. Linker, Tetrahedron 51 (1995) 9917;
(b) T. Linker, B. Kersten, U. Linker, K. Peters, E.-M. Peters, H.G. von Schnering, Synlett (1996) 468.
[8] (a) A.L.J. Beckwith, Tetrahedron 37 (1981) 3073;
(b) T.V. RajanBabu, Acc. Chem. Res. 24 (1991) 139.
[9] (a) D.D.M. Wayner, D.J. McPhee, D. Griller, J. Am. Chem. Soc. 110 (1988) 132;
(b) D.D.M. Wayner, A. Houmam, Acta Chem. Scand. 52 (1998) 377.
[10] T. Linker, K. Hartmann, T. Sommermann, D. Scheutzow, E. Ruckdeschel, Angew. Chem. Int. Ed. Engl. 35 (1996) 1730.
[11] (a) B. Giese, Angew. Chem. Int. Ed. Engl. 24 (1985) 553;
(b) E. Baciocchi, B. Giese, H. Farshchi, R. Ruzziconi, J. Org. Chem. 55 (1990) 5688.
[12] (a) M. Chmielewski, Z. Kaluza, C. Belzecki, P. Salanski, J. Jurczak, Tetrahedron Lett. 25 (1984) 4797;
(b) R.L. Halcomb, S.J. Danishefsky, J. Am. Chem. Soc. 111 (1989) 6661.
[13] (a) R.J. Ferrier, N. Prasad, J. Chem. Soc. Sect. C (1969) 581;
(b) K. Inaba, S. Matsumura, S. Yoshikawa, Chem. Lett. (1991) 485;
(c) B. Fraser-Reid, Acc. Chem. Res. 29 (1996) 57.
[14] (a) C. Einhorn, J. Einhorn, J.-L. Luche, Synthesis (1989) 787;
(b) J.M. Pestman, J.B.F.N. Engberts, F. de Jong, Recl. Trav. Chim. Pays-Bas 113 (1994) 533.
[15] (a) M. Allegretti, A. D'Annibale, C. Trogolo, Tetrahedron 49 (1993) 10705;
(b) A. D'Annibale, C. Trogolo, Tetrahedron Lett. 35 (1994) 2083.
[16] T. Linker, U. Linker, Angew. Chem. Int. Ed. Engl. 39 (2000) 902.
[17] J. Yamawaki, S. Sumi, T. Ando, T. Hanafusa, Chem. Lett. (1983) 379.
[18] (a) G.A. Molander, Chem. Rev. 92 (1992) 29;
(b) K. Rück, H. Kunz, J. Prakt. Chem. 336 (1994) 470.
[19] R.U. Lemieux, R.M. Ratcliffe, Can. J. Chem. 57 (1979) 1244.
[20] T. Linker, T. Sommermann, F. Kahlenberg, J. Am. Chem. Soc. 119 (1997) 9377.
[21] B. Giese, J. Dupuis, Angew. Chem. Int. Ed. Engl. 22 (1983) 622.
[22] T. Linker, T. Sommermann, T. Gimisis, C. Chatgilialoglu, Tetrahedron Lett. 39 (1998) 9637.
[23] V. Gyóllai, D. Schanzenbach, L. Somsák, T. Linker, Chem. Commun. (2002) 1294.